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Meta-Analysis of Cell Therapy Studies in Heart Failure and Acute Myocardial Infarction

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Abbreviations

ACCRUE	Meta-Analysis of Cell-based CaRdiac studies
AMI	Acute Myocardial Infarction
AP	Angina pectoris
BMMNCs	Bone Marrow Mononuclear Cells
BMMSCs	Bone Marrow-derived Mesenchymal Stromal Cells
BMSCs	Bone Marrow Stem Cells
CVD	Cardiovascular Disease
CIHD	Coronary Ischemic Heart Disease
G-CSF	Granulocyte-colony stimulating factor
EF	Ejection Fraction
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
IC	Intra-coronary
ICMJE	International Committee of Medical Journal Editors
ICMP	Ischemic Cardiomyopathy
IHD	Ischemic Heart Disease
IM	Intra-muscular
IPD	Individual Patient Data
IS	Information Size
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
MRI	Magnetic Resonance Imaging
MSCs	Mesenchymal Stromal Cells
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
RCTs	Randomized Controlled Trials
RRR	Relative Risk Ratio
TSA	Trials Sequential Analysis

Abstract

Heart failure is one the leading cause of death worldwide and has reached epidemic proportions in most industrialized nations. Despite major improvements in the treatment and management of the disease, the prognosis for patients with heart failure remains poor with approximately only half of patients surviving for five years or longer after diagnosis. The poor prognosis of HF patients is in part due to irreparable damage to cardiac tissue and concomitant maladaptive changes associated with the disease. Cell-based therapies may have the potential to transform the treatment and prognosis of HF through regeneration or repair of damaged cardiac tissue. Accordingly, numerous phase I and II randomized clinical trials have tested the clinical benefits of cell transplant, mostly autologous bone marrow-derived mononuclear cells, in patients with heart failure, ischaemic heart disease and acute myocardial infarction. Although many of these trials were relatively small, meta-analyses of cell-based therapies have attempted to apply rigorous statistical methodology to assess the potential clinical benefits of the intervention. As a prelude to larger phase III trials, meta-analyses therefore remain the obvious means of evaluating the available clinical evidence. Here, we review the different meta-analyses of randomized clinical trials that evaluate the safety and potential beneficial effect of cell therapies in heart failure and acute myocardial infarction spanning nearly two decades since the first pioneering trials were conducted.

Introduction

Cardiovascular disease (CVD), of which ischaemic heart disease (IHD) is a major component, is the leading cause of mortality accounting for approximately one third of deaths worldwide ¹. Although the death rate associated with IHD has gradually declined over the last fifty years the incidence and prevalence of heart failure (HF) is on the increase and has become almost a pandemic. Paradoxically, the Center for Disease Control and Prevention have recently reported an increase in the age-adjusted rate for HF-related mortality. ² The majority of treatment options in HF are palliative or aimed at slowing down disease progression (e.g. the prevention of cardiomyocyte loss or treatment of symptoms). In parallel to the increased incidence of HF, the use of new therapies such as coronary interventions, resynchronization therapy and the implantation of ventricular assist devices has also risen. As a consequence, hospitalisation due to HF has become more frequent, imposing a real economic burden on health care providers across the world. Therefore, there is an unmet clinical need to improve heart performance of patients who suffer IHD and HF and restore heart function.

Unlike many other tissues, heart muscle has a limited capacity to adequately repair itself after injury leading to progressive maladaptive remodelling and left ventricular dysfunction. Given the limited propensity for the heart to repair itself following injury, numerous strategies to repair or regenerate the damaged tissue have been proposed and tested in pre-clinical models and small to medium sized phase I and phase II clinical trials. ^{3, 4} One of the most promising strategies to repair or regenerate the damaged myocardium involves the use of cell-based therapies. Although several different experimental cell types have been tested in pre-clinical (animal) models and small scale clinical trials, the most commonly used cells are bone marrow-derived stem/progenitor cells (BMSCs) or bone marrow mononuclear cells (BMMNCs), derived from the patient's own bone marrow and are therefore an autologous cell transplant. Bone marrow is a heterogeneous tissue containing multiple cell populations of which approximately 1% are stem/progenitor cell populations of hematopoietic origin, multipotent mesenchymal stromal cells (MSCs) and endothelial progenitors. Unfractionated BMMNCs have been extensively used in clinical trials with the aim of repairing damaged heart tissue. Enriched populations of bone marrow-derived stem or progenitor cells can be isolated from BMMNCs using

antibodies against different cell surface antigens such as CD34 and CD133, through adaption to culture or by mobilisation into the peripheral blood stream following stimulation with cytokines such as G-CSF (Granulocyte-colony stimulating factor). In addition to BMSCs, other cell types such as skeletal myoblasts, adipose tissue-derived stem/progenitor cells, endothelial progenitors and cardiac progenitor cells have been tested in animal models and small clinical trials.³

All randomized control trials (RCTs) included in the meta-analyses described herein include a control arm(s) for each of the constituent trials. The control arm or placebo for many RCTs is often heterogeneous (no cells, unconditioned media or vehicle, mock injection etc.). Arguably the most appropriate control for these studies is to use irradiated bone marrow stem cells that are unable to replicate. Although not included in the meta-analyses described herein, Wollert and colleagues have recently published a RCT for myocardial infarction where γ -irradiated stem cells were included in one of the control arms of the trial.⁵ Importantly, this trial found that bone marrow stem cell therapy had no significant effect on LVEF improvement in patients treated with viable bone marrow stem cells compared to the control population that received irradiated cells.

The focus of this review is on the meta-analyses of RCTs for cell therapy in heart failure (HF) and acute myocardial infarction (AMI) using ostensibly autologous BMSC transplants.

Meta-analysis in preclinical models

Pre-clinical studies carried out in animal models present a unique opportunity to conduct homogenous trials, e.g. cell-treatment in a pre-specified time, similar animal strain and species, without confounding clinical factors. Recently, meta-analyses of a large number of pre-clinical studies of cell-based therapy in animal models of IHD have been published.⁶⁻⁹ Frequently, clinical outcomes (e.g. mortality) are not relevant in these studies, mostly due to the limited number of animals included in the studies and short follow-up times. However, efficacy parameters could be comparable to human clinical trials, especially in large animals where LV function and trial outcomes are measured using similar imaging modalities (e.g. magnetic resonance imaging or MRI). A meta-analysis of cell treatment studies in a mouse

model of myocardial ischemia, including only studies using cardiac MRI as functional analytic method of LV performance (21 randomized studies with a total of 583 mice), resulted in a significant improvement in LVEF of 8.59% as compared to the placebo-treated animals.⁷ Likewise, two meta-analyses of 52 and 82 large animal trials (pooling data from 888 and 1415 animals, respectively with iatrogenic ischemic heart disease reported an 8.3% LVEF benefit of cell-based therapy in contrast to control animals.^{6,8} Furthermore, a meta-analysis of cardiac progenitor cell (c-kit⁺, Sca-1⁺, cardiosphere and cardiosphere-derived cells) therapy studies in AMI (including 80 studies with 1970 rodents and large animals) reported a mean 10.7% LVEF increase in the cell-treated group compared to the control group.⁹ Interestingly, cardiac progenitor cell therapy led to a significantly higher effect in rodents than in large animals (increase of LVEF of 11.7% and 5.2% in small and large animals, respectively). The increase in LVEF following cell transplantation in large animals closely relates to the 5-7% improvement in LVEF observed in human clinical trials. Although Zwetsloot *et al.*, found that the large animal studies were superior in quality to their small animal counterparts, showed less evidence of publication and attrition biases, the differences in LVEF improvement between large and small animal pre-clinical models are not fully understood.⁹ While these unresolved differences may have a methodological or biological origin, it is noteworthy that the smaller effects on LVEF improvement in large animal studies are more closely reminiscent of the trial data derived from human subjects and as such may indicate that large animal are the more appropriate preclinical model for stem cell therapy for cardiac repair. In order to standardize animal studies and to avoid or reduce heterogeneity, and to draw more meaningful conclusions, the NHLBI-sponsored CAESAR consortium and the Working Group on Cellular Biology of the Heart of the European Society of Cardiology have suggested, that pre-clinical studies should also be performed as multi-center randomized blinded studies, similar to human clinical trials.^{10,11}

Meta-analyses of cell therapies in heart failure

Several small or medium-sized Phase I and II cell-based therapy studies have been conducted in HF patients. Currently, approximately 2300 patients with ischemic HF or chronic ischemic heart disease have been treated with different types of cells, mostly with autologous BMMNCs in 45 randomized trials. Other cell types, such as bone marrow-derived MSC, adipose tissue MSC, bone-marrow and peripheral blood

progenitor cells, cardiac progenitor cells (cardiospheres) or myoblasts were also used. HF patients with the characteristics of HFrEF (heart failure with reduced ejection fraction) can mostly be characterized by post-infarction ischemic cardiomyopathy with severe coronary artery disease. Therefore, intramyocardial delivery of cell, either by surgical or percutaneous intervention, seems to be the preferred route of delivery for the intervention. This is in contrast to patients with recent acute myocardial infarction (AMI) enrolled in cell therapy trials and who received cell treatment by intracoronary delivery.

Since the average number of participants in trials are rarely over 50, most of the cell-based therapy studies in HF patients are statistically underpowered. Due to the technical challenges of these trials, namely percutaneous or surgical intramyocardial cell delivery, patient enrolment in randomized trials is usually slow, commonly leading to premature study termination, and/or inconclusive trial results. Hence, systematic reviews and meta-analyses of cell-based regenerative therapies including larger numbers of patients are necessary to evaluate the clinical evidence of cell therapy interventions in this cohort of patients. Table 1 lists the characteristics and results of currently published meta-analyses that included randomized trials involving patients with signs of HF and aimed to assess the effect of cell-therapy on LVEF.¹²⁻²⁴ All trials included in these meta-analyses used autologous cells and no restriction was made with respect to the type of cells used. The summary table shows non-uniform patient populations, including also some studies with recent AMI or refractory angina. The majority of trials delivered the cells intramyocardially via percutaneous intervention. Understandably, therapeutic cell delivery requires coronary artery bypass surgery and injection of the cells into the non-revascularizable (hibernating) areas of the diseased myocardium. Furthermore, intracoronary cell infusion into selected arteries may not be sufficient in cases of multivessel disease or diffuse chronic ischemic myocardium. Most of the meta-analyses reported significant changes in left ventricular parameters (Table 2), namely left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV). However, the clinical outcomes of these meta-analyses are inconclusive (Table 1) since only 5 of the 13 meta-analyses reported a significant reduction in the risk of mortality in favour of the cell treatment in HF patients.^{19, 21-24}

Apart from 2 meta-analyses (Cheng *et al.*, 2013 and Fisher *et al.*, 2016), all studies reported a significant increase in LVEF in cell-treated patients compared to the control groups.^{18, 24} These discrepancies are potentially explained by differences in statistical power related to the sample size in each study. Cheng *et al.*, included only 5 RCTs in their meta-analysis and could therefore be under-powered to detect statistically significant changes in LVEF. Conversely, Fisher and colleague's meta-analysis included 1114 patients from 38 trials and would therefore have greater statistical power to detect an effect. It appears that with the inclusion of larger number of patients in the meta-analysis, the observed treatment effect on LVEF regresses to a point where the changes are no longer significant. Importantly, this finding is also observed in the largest meta-analyses for AMI.^{25, 26} Although LVEF is one of the most commonly used surrogate and prognostic markers in HF and an outcome measure in cell therapy RCTs, differences in the techniques used to measure LVEF are a source of heterogeneity when evaluating different studies.²⁷ Furthermore, the physiological and clinical significance of the small percentage changes in LVEF reported in most cell therapy RCTs has yet to be established.

Based on several pitfalls of the publication-based meta-analyses, namely the high heterogeneity of the trials, different follow-up times, doubled publications and mixed patient population, an individual data (IPD)-based meta-analysis of HF cell-based therapy trials would be desirable, such as the ACCRUE (Meta-Analysis of Cell-based CaRdiac stUdiEs) study in AMI patients.²⁵ The IPD-based meta-analysis of percutaneous intramyocardial delivery of regenerative cells in patients with HF is currently under statistical analysis, and some preliminary results have already been presented (Gyongyosi, unpublished data).

Meta-analysis of cell therapy trials in acute myocardial infarction

As is the case with HF and IHD, several small or medium-sized phase I and II cell-based therapy RCTs have been undertaken in patients with AMI. Currently, approximately 2700 patients have been included in meta-analyses of 41 RCTs of autologous cell therapy transplantation in AMI using predominantly BMSCs. It should be noted that many more AMI patients have been treated with cell therapies however, many RCTs and prospective uncontrolled studies do not meet the selection criteria for meta-analyses and were therefore excluded from further analysis. Patients

who suffered AMI underwent revascularization, mostly percutaneous coronary intervention or PCI, and received cell treatment following revascularization. Participants recruited to these trials presented LV dysfunction even after PCI and therefore, the rationale was that LVEF and LV volumes could be improved by cell transplantation. Therefore, changes in LVEF and LV volumes were the primary outcome of these trials. Cells were delivered mostly by infusion into the infarct-related coronary artery (intracoronary cell delivery).

Table 3 summarizes meta-analyses of bone marrow derived cell therapies for AMI published in the last 11 years. The first meta-analysis of cell therapy trials for AMI published in 2006 that included 482 patients enrolled in 5 RCTs, found a significant ($P = 0.04$) increase in LVEF between baseline and follow-up in the treatment group compared to controls but, more importantly, showed no difference in LVEF between treatment groups at follow-up, on average 5 months later.²⁸ By contrast, the first large scale meta-analysis of cell therapy for AMI collating data on 811 patients from 13 RCTs found a modest improvement in LVEF (2.99%), and a significantly reduced left ventricular end-systolic volume (LVESV) by 4.74 mL and myocardial lesion area by (3.51%) in patients treated with BMSCs compared to controls (Table 3). Subgroup analysis revealed that there was a statistically significant difference in LVEF in favour of BMSCs when cells were infused within 7 days following AMI and when the BMSC dose administered was higher than 10^8 cells. However, patients in the control group also showed a greater increase in LVEF if they were included into the trial within 7 days post-AMI.²⁵ In addition, the authors reported anecdotal trends in favour of benefit for most clinical outcomes examined, although none were statistically significant.

Meta-analysis of further trials incorporating increasing numbers of patients and longer follow-ups have produced largely similar results (Table 3), although their conclusions have been equivocal. Broadly speaking, these studies have reported modest but significant changes in LV function allied with no improvement in mortality in patients treated with cell therapies compared to the placebo arm of the trial. Larger meta-analyses such as those reported by Clifford *et al.*, and Zimmet *et al.*, found significant changes in LV function and LVEF (1.78%, Clifford *et al.*) measured using MRI, commonly regarded as the reference method for estimating LV volumes and

ejection fraction.^{29, 30} Although the improvements in LVEF may be statistically significant it is unlikely that these small changes are clinically relevant.

In addition to the clinical heterogeneity of these trials, early meta-analyses also observed statistical heterogeneity. Many of the larger meta-analyses in AMI have attempted to explain some of the heterogeneity associated with cell therapy for AMI, and have included subgroup analyses to examine the effects of different variables on LV function and clinical outcomes. For example, Delewi and colleagues found that intracoronary delivery of BMSCs led to a moderate improvement of LVEF and a reduction in recurrent AMI and readmission to hospital for heart failure, unstable angina or chest pain. Similarly, patients receiving intracoronary BMSCs within a 3 to 7 day window post-AMI were found have improved LVEF and decreasing end systolic and end diastolic volumes compared to patients treated within 24h or beyond 7 days after AMI suggesting that transplant timing may be a relevant source of heterogeneity in some meta-analyses.³¹ A recent meta-analysis focussing on cell therapy trials in both AMI and IHD collated data from 48 RCTs that enrolled a total of 2602 patients (n = 1954 for AMI and n = 648 for IHD) found that LVEF improved by 2.92% and reduced infarct size by 2.25%.³² The authors also concluded that BMSC therapy improved clinical outcomes, including all-cause mortality and recurrent myocardial Infarction, albeit with differences between AMI and CIHD diagnoses. For example, subgroup analysis found that although cell therapy did not reduce risk of mortality in AMI patients there was a significant reduction in deaths among patients with IHD.

Another major source of heterogeneity in RCTs and therefore subsequent meta-analyses is associated with biological properties or phenotypes of the cell populations used for transplantation. As mentioned above, heterogeneous cell populations have been used in clinical trials including unfractionated BMMNC, enriched CD34-positive or CD133-positive hematopoietic progenitor cells, peripheral blood-derived progenitor cells or bone marrow-derived MSCs. Data derived from the REPAIR-AMI trial suggested that basal migratory capacity or SDF-1 (stromal cell-derived factor-1) -induced migratory capacity of BMSCs may be associated with a range of clinical outcomes.³³ Assmus and co-workers found that the more migratory cells were associated with improved survival free of cardiac, cardiovascular,

unknown death, and re-hospitalization. Robust phenotypic differences in the ability of cardiosphere-derived cells from IHD patients to support vessel formation have recently been reported.³⁴ These data suggest that not all patients may be suitable for autologous cell transplants. Although current meta-analyses and their associated RCTs have yet to consider the phenotypes of the transplanted cells, this is clearly one of the major sources of trial heterogeneity and may explain why certain patients may benefit from some cell therapy while others do not.

In addition to BMSCs, a meta-analysis of cell therapies from AMI using MSCs has recently been published. Wang and colleagues (Table 3) analysed data from 8 studies containing a total of 449 participants treated with MSCs derived from bone marrow, adipose tissue and umbilical cord (allogenic) reporting no increase in LVEF in the treatment groups compared to controls.³⁵ Sub-group analysis found that transplantation time, route of delivery and cell dose may affect LVEF in AMI patients treated with MSCs. Specifically, the injection of no more than 10 million mesenchymal stromal cells, via percutaneous coronary intervention, improved left ventricular systolic function when administered within a week of AMI.

Individual patient data and trial sequential analysis

Prior to undertaking large scale clinical trials (Phase III), meta-analyses remain one of the most widely used methods to evaluate the benefit of a given intervention. However, findings derived from trial meta-analyses can be misleading if pitfalls in study designs, risk of reporting bias, and variation across studies are not carefully considered.^{36, 37} To address some of the limitations and inherent biases associated with meta-analysis of RCTs, meta-analyses of individual patient data (IPD) and trial sequential analysis (TSA) have recently been applied to AMI trials.^{25, 26, 38} In addition to summary statistics derived from meta-analyses of multiple trials similar analyses can be performed using IPD.³⁹ As its name suggests, IPD meta-analyses use prospective data derived from individual patients of all included studies removing the reliance on summary statistics for subsequent analyses. Thus, IPD-based meta-analyses contain transparent controlled data with unique definitions allowing data to be reanalysed *en masse*. Although IPD meta-analyses can help reduce bias associated with data analysis and reporting compared with trial meta-analyses, they cannot avoid bias or pitfalls associated with trial design. The first IPD-based meta-

analysis of cell therapy trials for AMI, ACCRUE (meta-Analysis of Cell-based CaRdiac stUdiEs), collated data from 12 RCTs containing 1252 individuals (767 receiving cell therapy and 485 controls) (Table 3).²⁵ In agreement with the largest trials-based meta-analyses described above, the ACCRUE study found that intracoronary cell therapy for AMI had no apparent benefit on left ventricular function (including measurements of LV function made by MRI) and clinical outcomes in the treated group compared to the untreated controls.

Trial sequential analysis (TSA) has been used to resolve some of the inherent problems associated with trial meta-analysis such as insufficient statistical power^{40, 41}. TSA leverages cumulative data to effectively reduce type I and type II errors and can be used to estimate information size (IS), similar to power calculations used in individual trials. Fisher and colleagues conducted a TSA on 41 AMI trials that included 2739 participants (Table 3).³⁸ All trials administered BM-derived cells (mononuclear cell, BMMSCs, hematopoietic progenitors, circulating progenitor cells). An '*a priori*' threshold of relative risk reduction (RRR) in mortality of 35% was established as similar figure was empirically associated to percutaneous coronary intervention (PCI) in AMI⁴². In summary, cell therapies as currently tested in clinical trials do not seem to have a beneficial effect on clinical outcomes when administered to AMI patients.

Based upon TSA for AMI, the required IS to detect an effect of 35% RRR in mortality in favour of cell treatment was estimated to be 4,055 participants. Similarly, the required IS to detect a 35% RRR of re-hospitalization was 3,392 participants. However, in practice many more patients will be required to detect smaller effect sizes. This study demonstrates that the current AMI RCTs and meta-analyses lack sufficient statistical power to detect clinically relevant outcomes explaining the inconsistent findings reported in different RCTs and their earlier meta-analyses that used shorter follow-up times.

Concluding remarks

Most meta-analyses reviewed herein seem to agree that the potential beneficial effect of cell therapies for HF and AMI is still inconclusive and statistically underpowered. In AMI, trial meta-analyses (including TSA) and IPD-based meta-

analysis have drawn similar conclusions suggesting that cell-based therapies for AMI had no apparent clinical benefit. In addition, several recently published large RCTs, that have yet to be included in meta-analyses, enrolling patients with ischemic HF and AMI, published neutral results regarding changes in LVEF between the cell treated and control groups.^{5, 43-45} Furthermore, the recently published global position paper on cardiovascular regenerative medicine stated that, even if cell-based therapy in HF patients proved to be safe, the results are neither positive nor consistent.⁴⁶

In addition to the concerns regarding statistical power, the quality of the evidence in meta-analyses is confounded by two major sources of variation: (i) pitfalls in trial design and (ii) inconsistencies reporting and interpreting trial results. Therefore, there is a need for trial standardization and deep data sharing to improve reproducibility. To this end, the ACCRUE consortium and guidelines published by the International Committee of Medical Journal Editors (ICMJE) recommend data sharing on publication of trial results (e.g. sharing of the de-identified IPDs in a confidential form within 6 months of the publication).^{47, 48} These efforts will hopefully resolve the majority of the controversies in data interpretation and therefore will direct future clinical trials.

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Table 1. Meta-analyses of human randomized clinical trials including patients with ischemic heart failure using autologous cells.

HF trials	No. of studies	Patients treated/controls	Patient population	Mortality	Application (No. of trials)	Conclusion
Brunskill <i>et al.</i> 2009 ¹²	21	565 / 526	AMI, CIHD	n/r	i.m. surgical (4), i.m. perc.(1), i.c. (17)*	only i.m. delivery was effective
Jiang <i>et al.</i> 2010 ¹³	18	490 / 490	AMI, CIHD	n.s.	i.m. surgical (2), i.c. (16)	cell therapy was effective only in patients with AMI
Donndorf <i>et al.</i> 2011 ¹⁴	6	94 / 85	CIHD	n.s.	i.m. surgical (6)	safe and effective
Zhao <i>et al.</i> 2011 ¹⁵	10	250 / 207	CIHD	n/r	i.m. surgical (5), i.c. (6)*	cell therapy was effective only with CABG but not with PCI
Wen <i>et al.</i> 2012 ¹⁶	13	378 / 280	IHD, HF	n/r	i.m. surgical (4), i.m. perc. (6), i.c. (4)*	cell therapy is more effective in patients with IHF
Kandala <i>et al.</i> 2013 ¹⁷	10	283 / 236	ICMP	n.s.	i.m. surgical (7), i.c. (4)*	cell more effective with i.m. delivery
Cheng <i>et al.</i> 2013 ¹⁸	5	135 / 75	Ischemic HF	n.s.	i.m. surgical (1), i.m. or perc. (4)	6 min walking distance † NYHA decrease †
Fisher <i>et al.</i> 2014 ¹⁹	23	659 / 478	CIHD, HF	sig.	i.m. surgical (3), i.m.perc. (9), i.c. (12)*	NYHA class and rehospitalization sig.
Xiao <i>et al.</i> 2014 ²⁰	20	453 / 322	CIHD	n.s.	i.m. surgical (8), i.m. perc.(8), i.c. (5)*	route of delivery, baseline EF and type of cells influence significance
Xu <i>et al.</i> 2014 ²¹	19	440 / 309	CIHD	sig.	i.m. surgical (7), i.m. perc.(7), i.c. (6)*	safe and effective
Tian <i>et al.</i> 2014 ²²	11	272 /220	CIHD	sig.	i.m. surgical (5), i.m. perc. (6)	more effective if revascularization was possible
Fisher <i>et al.</i> 2015 ²³	31	626 / 895	HF	sig.	i.m. surgical (7), i.m. perc.(12), i.c. (12)	sig. for rehospitalization
Fisher <i>et al.</i> 2016 ²⁴	38	1114 / 793	CIHD, HF, refractory AP	sig.	i.m. surgical (7), i.m. perc (17), i.c. (13)	low quality of evidence

Abbreviations: AMI, acute myocardial infarction; AP, angina pectoris; CABG, coronary artery bypass graft; CIHD, chronic ischemic heart disease; HF, heart failure; ICMP, ischemic cardiomyopathy; i.c., intracoronary application; i.m., intramyocardial; n/r, not reported; n.s., not significant; NYHA, New York Heart Association; perc., percutaneous; * including trials with more than one delivery route; † statistical significance between groups in subgroup analyses.

Table 2. Results of the left ventricular function parameters in meta-analyses including patients with ischemic heart failure.

HF trials	Patient population	LVEF difference (%)	LVESV difference (mL)	LVEDV difference (mL)
Brunskill <i>et al.</i> 2009 ¹²	CIHD	3.71*	n/r	n/r
Jiang <i>et al.</i> 2010 ¹³	AMI and CIHD	2.93*	-10.67*	8.61*
Donndorf <i>et al.</i> 2011 ¹⁴	CIHD	5.4*	n.s.	9.55
Zhao <i>et al.</i> 2011 ¹⁵	CIHD	4.59*	-0.36*	-0.38*
Wen <i>et al.</i> 2012 ¹⁶	IHD and HF	3.83*	-16.29	-13.76
Kandala <i>et al.</i> 2013 ¹⁷	ICMP	4.48*	-20.64*	-16.71*
Cheng <i>et al.</i> 2013 ¹⁸	Ischemic HF	0.11 (n.s.)	n/r	n/r
Fisher <i>et al.</i> 2014 ¹⁹	CIHD and HF	2.62*	-14.64*	n.s.
Xiao <i>et al.</i> 2014 ²⁰	CIHD	3.05*-3.35*	-11.75*	-7.8*
Xu <i>et al.</i> 2014 ²¹	CIHD	3.54*	-8.96*	-0.75
Tian <i>et al.</i> 2014 ²²	CIHD	4.91*	-10.66*	-7.82
Fisher <i>et al.</i> 2015 ²³	HF	4.02 - 4.66*	n/r	n/r
Fisher <i>et al.</i> 2016 ²⁴	CIHD, HF, refractory AP	-1.6 (n.s.)	n/r	n/r

Abbreviations: AMI, acute myocardial infarction; AP, angina pectoris; CIHD, chronic ischemic heart disease; HF, heart failure; ICMP, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; n/r, not reported; n.s., not significant; * p<0.05.

Table 3. Meta-analyses of human randomized clinical trials for patients with acute myocardial infarction.

AMI Trials	Sample Size (No. of studies)	Follow-up (months)	Mortality	LVEDV changes (mL)	LVESV changes (mL)	% change in EF (by MRI)
Hristov <i>et al.</i> 2006 ²⁸	482 (5)	4–6	n/r	n/r	n/r	n/r
Lipinski <i>et al.</i> 2007 ⁴⁹	698 (10)	6	n.s.	-4.6	-7.4*	n/r
Martin-Rendon <i>et al.</i> 2008 ⁵⁰	811 (13)	3–6	n.s.	-2.47	-4.74*	n/r
Zhang <i>et al.</i> 2009 ⁵¹	525 (6)	5	n/r	-0.15	n/r	n/r
Zhang <i>et al.</i> 2009 ⁵²	660 (7)	6	n.s.	-0.15	-0.25*	n/r
Bai <i>et al.</i> 2010 ⁵³	814 (10)	6	n/r	n/r	n/r	n/r
Kuswardhani and Soejitno 2011 ⁵⁴	906 (10)	4–60	n.s.	-3.08*	-5.52*	n/r
Takagi and Umemoto 2011 ⁵⁵	877 (15)	n/r	n/r	-0.18*	-0.35*	nr
Clifford <i>et al.</i> 2012 ²⁹	1765 (33)	<12	sig.	-3.52*	-4.47*	1.78*
Zimmet <i>et al.</i> 2012 ³⁰	1830 (29)	3–6	n.s.	-3.39*	-3.51*	n/r
Delewi <i>et al.</i> 2013 ⁵⁶	1641 (16)	3–6	n/r	n/r	n/r	0.16*
Chen <i>et al.</i> 2013 ⁵⁷	510 (5)	n/r	n/r	-2.29	-4.47	n/r
Jeong <i>et al.</i> 2013 ⁵⁸	1072 (17)	3–6	n/r	-3.46	-4.98*	n/r
de Jong <i>et al.</i> 2014 ⁵⁹	1513 (22)	6	n.s.	-2.8	-4.05*	0.13 (n.s.)
Liu <i>et al.</i> 2014 ⁶⁰	262 (8)	6–24	sig.	0.69	-0.99	n/r
Fisher <i>et al.</i> 2015 ²⁶	2732 (41)	6–60	n.s.	n/r	n/r	1.05 (n.s.)
Gyöngyösi <i>et al.</i> 2015 (IPD) ²⁵	1275 (12)	12	n.s.	1.2	0.4	n/r
Cong <i>et al.</i> 2015 ⁶¹	1318 (17)	12	n.s.	-1.69	-3.92*	n/r
Wang <i>et al.</i> 2017 (MSC) ³⁵	449 (8)	1–24	n/r	n/r	n/r	n/r
Xu <i>et al.</i> 2017 ³¹	2307 (34)	3–61	n.s.	n/r	n/r	n/r

Abbreviations: AMI, acute myocardial infarction; EF, ejection fraction; HF, heart failure; IPD, individual patient data; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MSC, mesenchymal stem cells; MRI, magnetic resonance imaging; n/r, not reported; n.s., not significant; * p<0.05.